Clinical Observations

Assessment of Clinical Effect of Therapy Combining Disease with Syndrome on Rheumatoid Arthritis

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Objective: To observe the effectiveness and safety of a therapy combining disease with syndrome on rheumatoid arthritis.

Methods: Eighty patients with rheumatoid arthritis belonging to syndrome of damp-heat obstruction were randomly divided into a treatment group and a control group according to stratified blocked randomization method.Forty cases in the control group orally took Loxoprofen Sodium Tablet and Leifumite Tablet and the other 40 cases in the treatment group orally took a Chinese medicine for 12 weeks as a course of treatment. ACR therapeutic effect was used as the standard for evaluating the total therapeutic effect.

Results: After 12 weeks of treatment, there was a statistical difference (P<0.01) in the improvement of VAS score, morning stiffness time, number of swelling joints, index of swelling joints, number of joints with tenderness, index of joints with tenderness, average grip strength of both hands, DSA28 score, HAQ, patient's assessment, physician's assessment, ESR, CRP and RF in both groups. The improvement of morning stiffness time, number of swelling joints, index of swelling joints, grip strength, HAQ and patient's assessment in the treatment group was much better than that in the control groups with statistical difference (P<0.05). ACR20, ACR50 and ACR70 was 27.5% (11/40), 37.5% (15/40) and 22.5% (9/40) respectively in the treatment group and 40% (16/40), 27.5% (11/42) and 10.0% (4/40) respectively in the control group with statistical difference (P<0.05) in the superiority of the treatment group over the control group. The incidence of adverse reaction in the control group was higher than that in the treatment group (P<0.05).

Conclusion: Definite therapeutic effect and high safety can be achieved in using the therapy combining disease with syndrome to treat rheumatoid arthritis belonging to syndrome of damp-heat obstruction.

Keywords: *combination of disease with syndrome; rheumatoid arthritis; syndrome of damp-heat obstruction*

The main pathological changes in rheumatoid arthritis (RA) are manifested in hyperplasia of synovial tissue in joints, infiltration of a large number of inflammatory cells, progressive destruction of cartilage and vasculitis outside joints. The whole course of disease is comprehensively manifested in the 3 pathological processes of hyperplasia, inflammation and autoimmune of synovial tissue.[1] Non-steroidal anti-inflammatory drugs can relieve symptoms of joints and alleviate sufferings of patients, and illness-condition-improving drugs can delay the development of illness condition.[2] TCM holds that RA belongs to the category of Bi (arthralgia) syndrome, which should be mainly treated according to symptoms and signs. Pathogeneses and prognoses for various diseases of Bi syndrome differ enormously. If the treatment is not focused on symptoms and signs, the therapeutic effects on RA will be greatly different. Pharmacological researches into Chinese drugs have shown that many Chinese drugs have the effects of eliminating inflammation, stopping pain and inhibiting immune. Under the guidance of TCM therapy on syndrome differentiation, to correctly select recipes of Chinese drugs with the effects of eliminating inflammation and inhibiting immune to treat RA (namely, to use therapy combining disease with syndrome to treat RA) will surely be able to greatly enhance the therapeutic effect of TCM on RA.[3] In order to verify the effectiveness of therapy combining disease with syndrome, the authors have carried out a random contrast research into RA patients with the most commonly seen syndrome of damp-heat obstruction. The result of the research is reported as follows.

METHODS

General Data

Eighty RA patients with the syndrome of damp-heat

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obstruction at the Third Hospital of Beijing University (28 cases), Beijing Military General Hospital (28 cases) and Wangjing Hospital of China Academy of Chinese Medical Sciences (24 cases) from June 2008 to December 2009 were randomly divided into a treatment group and a control group according to stratified blocked randomization method. The study was carried out with the approval from the Ethics Committee of The Third Hospital of Beijing University. Informed consent was obtained from all the study subjects.

Method of Administration

Patients in the control group orally took Loxoprofen Sodium Tablet 60 mg, 3 times a day, and Methotrexate 10–15 mg, once a week. Patients in the treatment group orally took a Chinese medicinal decoction of the therapy combining disease with syndrome on the basis of the above-mentioned treatment. The recipe consisted of Lao Guan Cao (Herba Erodii seu Geranii) 15 g, Chuan Shan Jia (Squama Manitis) 15 g, Xi Xian Cao (Herba Siegesbeckiae) 15 g, Tu Fu Ling (Rhizoma Smilacis Glabrae) 15 g, Hu Zhang (Rhizoma Polygoni Cuspidati) 15 g, Sheng Di Yu (Radix Sanguisorbae) 15 g, Xu Chang Qing (Radix Cynanchi Paniculati) 10 g and Ma Huang (Herba Ephedrae) 5 g. The decoction was orally taken one dose a day in two times. A course of treatment lasted 12 weeks in both groups.

Indexes for Observation

Clinical index: Clinical indexes under observation before and after treatment are number of swelling joints and index of swelling joints (28 joints are considered. Swelling classification is marked with the score of 0, 1 and 2, which is multiplied by the number of swelling joints), number of joints with tenderness and index of joints with tenderness (tenderness classification is marked with the score of 0, 1, 2 and 3, which is multiplied by the number of joints with tenderness), average grip strength of both hands, morning stiffness, VSA score, DAS28 score, HAQ (health assessment questionnaire), patient's assessment and physician assessment.

Laboratory index: Laboratory index includes blood routine, urine routine, hepatic function (ALT and AST), renal function (Cr and BUN), erythrocyte sedimentation rate (ESR), C reaction protein (CRP) and rheumatoid factor (RF).

Standard of Diagnosis

Standard of diagnosis in Western medicine:

All the patients under observation conformed to the standard of classifying RA stipulated by US Rheumatism Association in 1987:[4] 1) Morning stiffness lasts at least 1 hour (>6 weeks). 2) Swelling occurs in 3 or more joints (>6 weeks). 3) Swelling occurs in joints of the wrist, palm and near-end fingers (>6 weeks). 4) Swelling occurs in symmetric joints (>6 weeks). 5) Nodes occur under the skin. 6) Changes can be seen in roentgenogram of hands (at least showing osteoporosis and narrowed joint gap. 7) Rheumatoid factors are positive (titer >1:32). Patients conforming to 4 or more of the above-mentioned 7 items can be diagnosed as suffering from rheumatoid arthritis.

Standard of diagnosing the syndrome of damp-heat obstruction in TCM[5]: Major symptoms are swelling pain and hot sensation in joints, fever, limited flexion and extension of joints and morning stiffness. Minor symptoms are thirst, perspiration, deep yellow urine, dry stool, red tongue with yellow, thick and greasy fur, and slippery and rapid or wiry and rapid pulse.

Standard of Inclusion

Patients are 18–70 years old, conform to 1–3 grade in roentgenogram grading and sign an agreement of knowing condition of clinical research.

Standard of Exclusion

1) Patients have severe diseases of the liver, kidney, cardiac and cerebral blood vessels, respiratory system, blood and endocrine. 2) Patients have active gastrointestinal diseases. 3) Women are in pregnancy or in lactation period. 4) Patients are sensitive to any drug in the recipe.

Standard of Judging Therapeutic Effect

The therapeutic effect is judged with ACR20, ACR50 and ACR70 stipulated by US Rheumatoid Association.[6] ACR20 is defined as follows. Swelling and tenderness in 28 joints are alleviated by 20% and there is 20% improvement in at least 3 of the following 5 items: 1) rest pain, 2) daily life ability, 3) physician's assessment, 4) patient's assessment and 5) reaction substances (ESR or CRP) at acute stage. ACR50 and ACR70 are defined as improvement by 50% and 70% respectively according to the same standard.

Statistical Method

SAS8.0 statistical software is used for processing data, which are expressed with $\bar{x} \pm s$. *T* test is used to compare measurement data conforming to normal distribution between the two groups. Wilcoxon test is used to compare measurement data not conforming to normal distribution. *Chi*-square test is used to compare enumeration data. Ridit analysis is used for classified data. Obvious bound is determined as 0.05.

RESULTS

Comparison of Baseline Data between the 2 Groups

Among the 40 cases in the treatment group were 11 males and 29 females aged 49.0±12.6 with their illness course of 32.5±28.0 months. Among the other 40 cases in the control group were 12 males and 28 females aged 52.6±10.1 with their illness course of 38.0±24.3 months. There was no statistical difference in sex, age, illness course, illness condition and other baseline data between the two groups (P>0.05, Table 1).

Comparison of Clinical and Laboratory Indexes before and after Treatment in the 2 Groups

After 12 weeks of treatment, there were statistical differences (P<0.01) in the improvement of VAS score, morning stiffness time, number of swelling joints, index of swelling joints, number of joints with tenderness, index of joints with tenderness, grip strength, DAS28 score, HAQ, patient's assessment, physician's assessment, ESR, CRP and RF in the 2 groups. The improvement of VAS score, morning stiffness time, number of swelling joints, index of swelling joints, number of joints with tenderness, index of joints with tenderness, grip strength, DAS28 score, HAQ, patient's assessment and ESR in the treatment group was better than that in the control group with statistical difference (P<0.05, Table 1).

Table 1. Comparison of clinical and laboratory indexes before and after treatment in the 2 groups ($\bar{x} \pm s$)

Item	Treatment group (40 cases)		Control group (40 cases)		T	P value
	Before treatment	After treatment	Before treatment	After treatment		
VAS (10 cm)	6.80±1.60	3.65±1.28△	6.17±1.18	3.53±1.11△	2.149	0.036▲
Morning stiffness (min)	124.33±83.73	42.33±21.68△	102.81±78.45	54.69±33.43△	2.078	0.043▲
Number of swelling joints	11.83±5.91	3.07±1.11△	12.09±7.10	17.88±6.11△	2.037	0.046▲
Index of swelling joints	29.73±11.78	10.37±3.48△	31.47±16.13	17.88±6.11△	2.071	0.043▲
Mumber of joints with tenderness	17.37±8.43	5.77±1.94△	16.53±6.23	8.44±2.51△	2.073	0.043▲
Index of joints with tenderness	27.77±9.35	15.40±6.33△	26.94±8.38	8.44±2.51△	2.091	0.041▲
Grip strength (mmHg)	71.80±45.02	113.33±39.32△	86.00±38.96	121.02±38.86△	2.087	0.041▲
DAS28 score	6.13±1.53	3.83±1.21△	5.72±2.02	3.81±1.69△	2.502	0.015▲
HAQ	1.87±0.68	0.67±0.66△	1.78±0.75	0.81±0.74△	2.870	0.007★
Patient's assessment	6.13±1.57	2.87±1.04△	5.91±1.92	3.19±1.33△	2.771	0.007★
Physician's assessment	6.90±1.32	2.93±0.83△	6.69±1.69	3.22±1.07△	2.497	0.797
ESR (mm/h)	45.40±24.34	18.53±9.47△	41.44±23.13	23.66±10.17△	2.037	0.046▲
CRP (mg/L)	27.51±30.98	7.83±4.66△	25.98±31.93	11.09±7.82△	0.707	0.482
RF (IU/mL)	129.22±82.99	37.43±17.51△	118.66±109.53	43.41±23.47△	0.807	0.423

Notes: △P<0.01 as compared to the datum before treatment in the same group; ▲P<0.05 as compared to the difference with the datum in the control group; *P<0.01 as compared to the difference with the datum in the control group.

Comparison of ACR Therapeutic Effects between the 2 Groups

The ACR therapeutic effect in the treatment groups was better than that in the control group with statistical difference (P<0.05, Table 2).

Adverse Reaction

The incidence of adverse reaction in the control groups was higher than that in the treatment group with statistical difference (P<0.05, Table 3).

Table 2. Comparison of ACR therapeutic effects between the 2 groups（Cases (%)）

Group	Cases	<ACR20	ACR20	ACR50	ACR70	χ^2	P value
Treatment group	40	5 (12.5)	11 (27.5)	15 (37.5)	9 (22.5)	3.8588	0.0358
Control group	40	9 (22.5)	16 (40.0)	11 (27.5)	4 (10.0)	-	-

Table 3. Comparison of incidence of adverse reaction between the 2 groups（Cases (%)）

Group	Cases	Reduction in white cells (%)	Damage to hepatic function (%)	Gastrointestinal reaction (%)	Others (%)	Total (%)	χ^2	P value
Treatment group	40	1 (3.33)	0 (0.00)	1 (3.33)	0 (0.00)	2 (6.67)		
Control group	40	3 (9.38)	1 (3.13)	3 (9.38)	1 (3.13)	8 (25.00)	3.8472	0.0498

DISCUSSION

TCM holds that RA belongs to the category of Bi syndrome. Since ancient time, treatment according to symptoms and signs has been used as TCM therapeutic principle. However, RA and common Bi syndrome differ in nature not only in pathogenesis but also in prognosis. Bi syndrome may be effectively treated with a method to eliminate inflammation and stop pain. However, RA belonging to a lifelong immune disease should be treated with immune inhibition to control the development of illness. Therefore, treatment should be focused on symptoms and signs in treating RA, that is to say, the

treatment according to symptoms and signs should be based on pharmacological researches into Chinese drugs and on RA-treating concept in Western medicine. In the past several decades, great progress has been made in pharmacological researches into Chinese drugs, providing energetic support for the therapy combining disease with syndrome.

In this research focusing on the most commonly seen RA syndrome of damp-heat obstruction, the authors explored the effectiveness and safety of the therapy combining disease with syndrome on RA. The result of the research showed that after 12 weeks of treatment, there was statistical significance (P<0.01) in the improvement of VAS score, morning stiffness time, number of swelling joints, index of swelling joints, number of joints with tenderness, index of joints with tenderness, grip strength, DAS28 score, HAQ, patient's assessment, physician's assessment, ESR, CRP and RF in the 2 groups. The improvement of VAS score, morning stiffness time, number of swelling joints, index of swelling joints, number of joints with tenderness, index of joints with tenderness, grip strength, DAS28 score, HAQ, patient's assessment and ESR in the treatment group was better than that in the control group with statistical difference (P<0.05). ACR therapeutic effect in the treatment group was also better than that in the control group (P<0.05). The incidence of adverse reaction in the control group was much higher than that in the treatment group (P>0.05), indicating that TCM therapy combining disease with syndrome has definite therapeutic effect and high safety in the treatment of RA.

In the recipe, Xi Xian Cao (Herba Siegesbeckiae) can inhibit the generation of IL-1 in rats with arthritis, thus preventing IL-1 from damaging the cartilage and bone in joints of rats, alleviating the process of whole and local pathological changes, and having obvious analgesic effect.[7] Total tannins of Lao Guan Cao (Herba Erodii seu Geranii) has the effects of eliminating inflammation, inhibiting immune and stopping pain.[8] Saponins of Chuan Shan Jia (Squama Manitis) has obvious effect of inhibiting the immune function of body fluid and cell.[9] Tu Fu Ling (Rhizoma Smilacis Glabrae) can obviously inhibit the swelling in feet of rats with arthritis and noticeably reduce the frequency of body-twisting reaction of mice, indicating that Tu Fu Ling has obvious anti-inflammatory and analgesic effects.[10] Hu Zhang (Rhizoma Polygoni Cuspidati), Sheng Di Yu (Radix Sanguisorbae), Xu Chang Qing (Radix Cynanchi Paniculati) and Ma Huang (Herba Ephedrae) have anti-inflammatory and analgesic effects to different extent.[11-14] Xi Xian Cao, pungent and bitter in taste and dispersive and dry in nature, acts as a monarch drug to remove damp-heat, eliminate rheumatism, relieve arthralgia and stop pain. Lao Guan Cao and Chuan Shan Jia act as minister drugs to dispel wind, remove dampness, relax muscles, clear collaterals and treat heat arthralgia. Tu Fu Ling, sweet in taste, can eliminate toxin, remove dampness and disperse damp-heat from lower jiao. Hu Zhang, better in taste and cold in nature, is good at eliminating toxin, repelling dampness, promoting blood circulation and removing blood stasis. Sheng Di Yu, bitter in taste and slightly cold in nature, can remove toxin and clear away heat from blood. Xu Chang Qing and Ma Huang, pungent in taste and dispersive in nature, can dispel wind and dampness from the body surface and restrict the above-mentioned drugs, bitter in taste and cold in nature, from damaging yang-*qi*. Xu Chang Qing, Ma Huang, Tu Fu Ling, Hu Zhang and Sheng Di Yu act as adjuvant and conductant drugs. All the drugs are used together to remove damp-heat and stop arthralgia- pain. The recipe is characterized by combination of differentiating disease with differentiating syndrome, embodying the wholeness and flexibility of treatment according to symptoms and signs, effectively treating dysfunction of immune, inflammatory reaction and other pathological changes, integrating the characters of treating RA in TCM with Western medicine and theoretically embodying the therapeutic thought of combination of TCM with Western medicine. Therefore, the therapy is worth further studying and popularizing.

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